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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
28 September 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INDUSTRIAL PROCESS FOR PREPARATION OF CLOPIDOGREL HYDROGEN SULPHATE

(57) Abstract: An improved process for the manufacture of Clopidogrel starting from 2-(2-thienyl) ethylamine, which eliminates the isolation of an unstable intermediate like 2-(2-thienyl) ethyl formimine by subjecting it to a one pot cyclization to get 4, 5, 6, 7-tetrahydrothieno (3,2-c) pyridine of Formula II and further reacting with halo-compound of Formula III (where X is Cl or Br) at 20 to 90°C temperature characterized in a solvent like water and/or dichloroethane in presence of organic or inorganic bases is disclosed herein. This invention further discloses a process for resolution of racemic Clopidogrel into its optical antipodes and converting the dextroclopidogetrel base into its known polymorphs namely 'Form I' or 'Form II' in solvents selected from methyl propyl ketone, methyl isopropyl ketone, diethyl ketone or their mixture thereof, mixture of ethyl acetate and methyl propyl ketone, mixture of ethyl acetate and methyl isopropyl ketone, or mixture of ethyl acetate and diethyl ketone or ethyl acetate.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN05/00071

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07D 409/04(2006.01);C07D 333/20(2006.01)

USPC: 546/114;549/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/114; 549/74

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	U.S. 5,132,435 A (BOUSQUET et al.) 21 July 1992 (21.7.1992), Column 3, lines 58-68 and Column 4, lines 1-39. See also Claim 6, Column 10.	1-14
X	US 4,847,265 B2 (BADORC et al.) 11 July 1989 (11.7.1989), Column 2, lines 10-60.	15-17
Y	U.S. 6,635,763 B2 (PANDEY et al.) 21 October 2003 (21.10.2003), Columns 25 and 30, Examples 38-41, Column 2, lines 21-29.	18-29
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X		
Y	WO 03/066637 A1 (EGIS GYOGYSZERGYAR RT) 14 August 2003 (14.8.2003) Page 8, Pages 18-21, Examples 1-6.	18-30
X	US 6,429,210 B1 (BOUSQUET et al.) 6 August 2002 (6.8.2002), Column 4, Tables 1 & 2.	30

☐ Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

17 June 2006 (17.06.2006)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN05/00071

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 30
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
It is not clear whether applicants are claiming a product or a method.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TN05/00071

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I, claim(s) 1-14, drawn to a process for the manufacture of clopidogrel.

Group II, claim(s) 15-17, drawn to a method of racemic resolution of clopidogrel.

Group III, claim(s) 18-20, drawn to a process for the manufacture of clopidogrel crystals, form I.

Group IV, claim(s) 21-24, drawn to a second process for the manufacture of clopidogrel crystals, form I.

Group V, claim(s) 25-29, drawn to a process for the manufacture of clopidogrel crystals, form II.

Group VI, claim(s) 30, drawn to clopidogrel hydrogen sulfate.

The inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. Although Groups I-VI share a common technical feature, they do not share a special technical feature, i.e. a contribution over the prior art. The common technical feature shared by all the groups is the chemical formula for clopidogrel. Clopidogrel, however, is not novel and therefore breaks unity. For example, some groups claim a crystal form of clopidogrel. In this case, the contribution over the prior art is the lattice structure of the new crystal and not the chemical formula, as the chemical formula is unchanged. If all groups shared the new crystal form (the contribution over the prior art) unity would exist. However, in this case, there is no contribution over the prior art linking the groups and therefore unity is lacking.